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Mortality from *Listeria monocytogenes* Meningoencephalitis following escalation Alemtuzumab Therapy for Relapsing-Remitting Multiple Sclerosis

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Summary

We report the case of a patient who died from the rare but increasingly recognised complication of Listeriosis in the immediate phase following Alemtuzumab escalation therapy one month after discontinuing dimethyl fumarate. There is considerable overlap with typical post-infusion symptoms therefore high surveillance and low threshold for empirical or possible prophylactic antibiotic therapy is advocated.

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Introduction

The benefits from large-scale use of potent immunomodulatory therapy for relapse suppression in multiple sclerosis are accompanied by an array of very real general and treatment-specific risks.

The use of the anti-CD52 humanised monoclonal antibody Alemtuzumab comes with a broad awareness and vigilance for well-recognised and largely delayed autoimmune complications (1-6) and the more immediate, infusion-related events that can be serious in approximately 3% of cases (2, 4, 7).

To date there have also been 4 reported cases of listeriosis which have resulted in syndromes of acute meningitis (8, 9) or listeriosis (10) with sepsis specifically during the broad immune-deplete phase in the days-weeks following completion of Alemtuzumab infusion cycles (10-13). Although approximately 9200 patients have now received this therapy for the indication of multiple sclerosis (14) suggesting this occurrence is relatively rare. A high index of suspicion and low threshold for intervention is required for listeriosis as its presentation may be clouded by common symptoms associated with Alemtuzumab. Furthermore, effective treatment is readily available but risk of immediate mortality is high.

We present the first case of mortality due to confirmed listeriosis which arose after completion of the first Alemtuzumab infusion

cycle and discuss some important considerations.

Case Description

A 42-year-old Caucasian lady was diagnosed with Relapsing Remitting multiple sclerosis in May 2014 after presenting with a central sensory syndrome. She gave a past history of diplopia in 1997. In May 2014 she experienced a sensory relapse. In March 2015 she developed impaired dexterity of her left hand consistent with relapse. Her MRI and CSF oligoclonal studies were supportive of an MS diagnosis meeting modified McDonald criteria (15) and she elected to commence dimethyl fumarate in July 2015.

This was well tolerated however new sensory disturbance arose in August 2015. Dimethyl fumarate was continued. She then had a further relapse in April 2016 when neurogenic pain and new sensory disturbance arose necessitating use of methylprednisolone. Predominant but incomplete recovery followed and consideration of escalating treatment began. After counselling regarding options available according to NICE Guidelines 2014 (16) the patient elected to pursue Alemtuzumab but wished to defer until after completing a family vacation.

Dimethyl Fumarate was discontinued in July 2016. Contemporaneous brain MRI showed stable appearances and her Expanded Disability Severity Scale score was 2.5, with Functional System Scores of Cerebral 2, Sensory 2, Sphincters 1, Cerebellar 1 and all else 0. Ambulation was unrestricted. The patient was symptomatic of noticeable short-term memory difficulties, neuropathic pain and fatigue. Her only other medical background included hypothyroidism. Medications included Levothyroxine 75 micrograms daily, Pregabalin 300mg twice daily, and Duloxetine 60mg daily.

One month after Dimethyl Fumarate cessation Alemtuzumab 12mg was administered intravenously for 5 days, with concurrent 1 gram Methylprednisolone intravenously for the first 3 days as per recommended delivery (17).

On the second day of administration low-grade and non-limiting headache symptoms were reported. In the absence of abnormal observations, constitutional upset or new neurological symptoms, administration continued uneventfully with eventual discharge on standard symptomatic and prophylactic medication.

Follow up blood count monitoring at day 5 post-completion revealed anticipated decrements in haematological indices [*see table 1*], with reported persistence of the same low-grade headache symptoms without pyrexia or wider features.

At day 6 post-completion, a 3 day history of diarrhoea and vomiting with general malaise was reported and healthcare provider review planned. Rapid deterioration supervened with the patient found in a pyrexial, unresponsive state at home with respiratory distress. Paramedic attenders found the patient comatose (GCS 7; E4, V2, M1) with severe tachypnoea (60 breaths/minute), high-grade pyrexia of 40^{o}C, tachycardia 176 bpm and a Blood Pressure of 152/96mmHg. She was intubated at the scene and transferred to hospital.

Volume resuscitation was commenced and broad coverage for unspecified sepsis syndrome in the context of immunosuppression initiated with Tazocin 4.5g, Gentamicin 400mg and Aciclovir 700mg intravenously. CT head revealed reduced grey-white differentiation, diffuse cerebral swelling, bilateral temporal horn distension and cisternal effacement [*see figure 1a*]

consistent with severe meningoencephalitis and precluding safe lumbar puncture for CSF study. Laboratory studies demonstrated a grossly elevated C reactive protein in the absence of a peripheral leucocytosis, typical of a Sepsis/Systemic Inflammatory Response Syndrome in the context of immunosuppression [*see table 1*].

Eight hours after admission her pupils became fixed and asymmetric. An external ventricular drain was placed in the right lateral ventricle to allow decompression of intracranial pressures recorded in excess of 30cmCSF. The CSF was clear and colourless, only 5 white cells, 279 red cells, protein of .33g/l and a raised glucose gradient of 2.8mmol/l in CSF vs. 8.1mmol/l in serum.

Antimicrobial therapy was switched to ceftriaxone 2g b.d. with aciclovir 700mg t.d.s. and with the suspicion of listeriosis, amoxicillin 2g four hourly was commenced.

Electroencephalography demonstrated a globally isoelectric recording and a full dependence on ventilator support ensued with loss of self-initiated respirations.

Repeat cranial CT imaging with angiographic sequences revealed severe global cerebral oedema with worsening cisternal effacement and generally poor angiographic flow and incipient herniation despite adequate positioning of the external ventricular drain [see figure 1b].

PCR on the CSF yielded a positive result for Listeria monocytogenes. Despite resolution of pyrexia and improving inflammatory indices a diagnosis of brain death was recorded at 60 hours following admission. Cultures of blood and CSF later supported the diagnosis of listeriosis.

Discussion

Although the risk of opportunistic and atypical infections in the context of immunosuppression is familiar, the particular vulnerability to listeriosis in the acute phase following Alemutuzumab administration is not broadly appreciated.

In this case as with others in the literature(10-13), the patient did not have clear exposure to foodstuffs classically associated with heightened listeria risk. The patient had been concordant with our local dietary guidelines (first two weeks post Alemtuzumab commencement) formally issued to patients undergoing Alemtuzumab therapy. At the time there was no mandatory SPC advice in Europe to avoid such foodstuffs (18). This has since changed as of June 2016 (17). Similarly with the other cases the timing appears, at least so far, specific to the period of maximum suppression of lymphocyte counts following the anti-CD52 effect (19).

Rau et al.(10) suggest that the listeriosis arising in these patients represents a reactivation of latent infection from possible reservoirs in the gallbladder or bone marrow tissues due to loss of the normal defence afforded by CD8 T cell cytotoxic effects, which are singularly important in host repulsion of listeria intracellular bacteria (10). As such, the required duration of dietary abstinence becomes far less clear. This may be particularly important in patients exposed to prior immunomodulatory therapies.

The typical CSF picture associated with listeria is one of marked neutrophilic pleocytosis, elevated protein and, where sampled, raised lactate. This is seen in 77% of cases (20), however this pattern may be absent and in this context of immunoparesis, the isolated hypoglycorrachia as seen here may be the

sole abnormality in addition to raised intracranial pressure (10).

It is recognised that while listerial meningitis produces the full constellation of febrile illness, with meningism, neurological deficit and sepsis syndrome, this often develops subacutely, with gastroenteritis and non-specific malaise dominating initially (10, 20). Timely diagnosis is further hindered by the prevalence, as seen in both trials and clinical practice, of near ubiquitous malaise, headache symptoms and low grade pyrexia with Alemtuzumab administration (2, 4, 11, 21).

The timing of listeriosis here in relation to therapy, as with the other reported cases, strongly suggests a causal relationship. However the timing and nature of prior disease modifying therapy is also an important consideration.

The decision to escalate from dimethyl fumarate to Alemtuzumab was stimulated by further clinical relapse activity whilst on the former. On the basis of published pharmacokinetic data for dimethyl fumarate (EMA Summary of Product Characteristics) a month-long period of washout was undertaken prior to Alemtuzumab initiation. The haematologic profile at baseline did demonstrate a very mild lymphopenia that was considered acceptable.

The time spent off therapy was considered to pose significant risk of further relapses and the hazards of irreversible damage or limiting function inherent to them. The phenomenon of 'rebound relapse' after disease modifying therapy discontinuation, or at least return to baseline relapse rates is well described (22-24).

Other reported cases of listeriosis/listeria meningitis have similarly affected individuals completing Alemtuzumab administration after experiencing relapsing disease uncontrolled by a range of licensed therapies with varying modes of action (10-13).

With the growing move toward '*No Evidence of Disease Activity*' as a treatment target and with no currently available therapy achieving this in more than 50% of patients over an initial 2 year period even with Alemtuzumab (25, 26) a growing number of patients will be deemed to require escalation. Despite the vast number of permutations of treatment combinations and their timings, MS physicians currently have comparatively little non-trial data on the risks thereof to guide informed decision making. Caution is therefore mandatory.

With respect to mitigating future risks of listeriosis with Alemtuzumab, dietary guidance alone may be insufficient and CSF analysis on all patients with headache is impractical and not without its own risk. We therefore advocate a high index of suspicion and low threshold for empirical therapy in all those with progressive systemic symptoms or headache, or fever in the days and weeks following Alemtuzumab administration to avoid further mortality from listeriosis in this context.

Alternatively, prophylactic cover of listeriosis using antibiotics such as Co-Trimoxazole, as used in other specialist areas using higher dose Alemtuzumab (27-29) could be considered. Although Co-Trimoxazole in itself may pose adverse reactions.

Conclusion

Alemtuzumab therapy appears to confer a specific vulnerability to *Listeria monocytogenes* infection. This led to mortality from a very rapidly progressive meningoencephalitis following otherwise

routine administration in a typical case of multiple sclerosis. Preceding disease modifying therapy may modify risk in a currently unquantified manner and high vigilance for this complication is needed. The speed of onset in this case should raise awareness of the need to see such patients without delay to minimise risk.

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